A pilot study of the effect upon multiple sclerosis of the menopause, hormone replacement therapy and the menstrual cycle

R Smith MRCP MRCOG **J W W Studd** MD FRCOG *King's College Hospital, Denmark Hill, London SE5 8RX*

Keywords: multiple sclerosis; menopause; oestrogen replacement therapy; menstrual cycle

Summary

A questionnaire enquiring about changes in severity of symptoms of multiple sclerosis with the menstrual cycle, menopause and use of hormone replacement therapy was answered retrospectively by 11 premenopausal and 19 postmenopausal women. Eighty-two per cent of menopausal women reported an increase in severity premenstrually. Of the postmenopausal women 54% reported a worsening of symptoms with the menopause, and 75% of those who had tried hormone replacement therapy reported an improvement. The results of this pilot study indicate the need for further research to clarify the effects of the menopause and hormone replacement therapy upon multiple sclerosis.

Introduction

The possibility that multiple sclerosis (MS) may be modulated by ovarian sex steroids, as are other disorders of supposed autoimmune aetiology[1], is strongly supported by data concerning the effect of pregnancy upon MS. The very high oestrogen levels found in the third trimester of pregnancy, if anything, bring about a reduction in the rate of relapse, whereas the sudden withdrawal of oestrogen characterizing the puerperium is associated with a two to three fold increase in relapse rate[2-4]. Fortunately the detrimental oestrogen deficiency of the puerperium is brought to an end by the return of cyclical ovarian activity, and so, overall, pregnancy has no effect upon the course of MS[4-6]. In contrast, the menopause, another state of physiological oestrogen withdrawal, is permanent. This observation begs the question as to whether the menopause is associated with a deterioration in MS, and what effect oestrogen replacement has upon the many manifestations of this condition. In the absence of any published data, we used a simple retrospective questionnaire to determine whether this question warrants further study. In addition, information was gathered concerning the menstrual cycle and MS, and the results are also presented.

Patients and methods

All female MS sufferers attending lectures at the annual general meeting of Action Research in Multiple Sclerosis were invited to fill out a questionnaire and return it by post. The questionnaire gathered data concerning age, menstrual cycle, menopausal age, use of contraception, HRT or other hormones, and duration of MS. An attempt to assess overall disease severity was made by asking the women to score their degree of disability (none=0, mild=1, moderate=2, severe=3) in each of six areas (strength, co-ordination, speech, sensation, bladder/bowel and sight) derived from the functional systems of the Kurtzke Disability Status Scale[7], and adding the scores. Any change in disease severity with either the menstrual cycle, menopause or HRT, was assessed by asking the women to score the degree of change in disability (much worse=2, slightly worse=1, no change=0, slightly better=−1, much better=−2) in each of the six functional systems, and adding the scores. A positive score indicating an increase in disability and a negative score a reduction in disability. Enquiry was made as to the presence and severity of menopausal symptoms.

Results

Nineteen questionnaires were completed by women considered to be postmenopausal or climacteric by virtue of either 6 months or more of amenorrhoea or the presence of hot flushes, and 11 by premenopausal women. The postmenopausal women had a mean age of 56.1 years, mean duration of MS of 17.4 years, and a mean total disability score of 7.5 (standard deviation 3.52). The mean score for change in disability with the menopause was +2.15 (SD 3.05, $n=13$), indicating an overall increase, 54% reporting a worsening of disability, 38% no change, and 8% an improvement. The mean score for change in disability with HRT was −2.88 (SD 2.64, $n=8$) indicating an overall reduction in disability, with 75% reporting an improvement and 25% no change. Eleven premenopausal women completed the questionnaire. They had a mean age of 35.8 years, a mean duration of MS of 11.3 years, and a mean total disability score of 6 (SD 3.26). The mean score for change in disability in the premenstrual phase was +1.9 (SD 3.18, $n=11$), indicating an overall increase in disability, with 82% reporting a deterioration and 18% an improvement (Table 1).

Table 1. Percentage of women reporting changes in severity of multiple sclerosis with the menopause, hormone replacement therapy or premenstrually

	Worse/more	*No change*	*Better/less*
With menopause	54%	38%	8%
With HRT	0	25%	75%
Premenstrually	82%	0	18%

Correspondence to: Dr Roger Smith, The Menopause Clinic, Dulwich Hospital, East Dulwich Grove, London SE22 8PT

0141-0768/92
100612-02/$02.00/0
© 1992 The Royal Society of Medicine

Discussion

These results do suggest that withdrawal of oestrogen at the menopause may be associated with a worsening of MS and that oestrogen replacement may have an opposite effect. It is possible to speculate as to why this might be so.

A role for autoimmunity in the aetiology of MS is suggested by its similarity to the immunologically mediated animal model experimental allergic encephalomyelitis, and by the finding of reduced levels of circulating suppressor T cells accompanying relapse[8]. Oestrogens may influence MS by modulating autoimmunity. For example pregnancy alters immune function, with absolute numbers and percentage of T helper cells being significantly reduced throughout, particularly in the third trimester, absolute numbers returning to normal within a month of delivery[9]. In addition it has recently been found that in postmenopausal women oestrogen treatment is associated with a depression of both delayed hypersensitivity and the mixed lymphocyte reaction[10]. Thus oestrogen may depress autoimmunity and thereby exert a beneficial effect upon MS. An alternative explanation is that the additional burden of menopausal symptoms may render the climacteric woman less able to cope with disability from MS, and hence this disability seems subjectively worse.

These results also suggest that premenopausal women may experience a subjective increase in severity of MS symptoms perimenstrually. Although the late luteal and early menstrual phases of the cycle are times of low oestrogen, the short time scale of these changes argues against an immunological cause. A possible explanation is simply that the presence of premenstrual symptoms at this time may make the same objective level of disability seem subjectively worse. A well known observation is that heat may temporarily increase the level of disability in MS[8]. It is possible that the elevation of basal body temperature accompanying ovulation might in a similar manner be responsible for a temporary increase in disability in the second half of the cycle. If this were true then suppression of ovulation should prove beneficial.

There are three main arguments why postmenopausal and climacteric women with MS may benefit from HRT. The first is straightforward, that 80% of untreated climacteric women experience symptoms of oestrogen deficiency, and in many these symptoms are severe[11]. HRT may thus prevent considerable and unnecessary morbidity, and by so doing may also enable these women to cope better with their disability. The second argument is that women with MS may especially benefit from HRT. Immobility, and treatment with steroids, will compound the risk of osteoporosis already associated with the menopause. Oestrogen will not only prevent further bone loss, but when given in the form of subcutaneous implants can actually replace bone mass previously lost[12]. In addition the substantial increases in both skin thickness and collagen content that occurs with oestrogen therapy may have a beneficial effect in preventing, or aiding healing of, pressure sores in the severely disabled patient[13]. Furthermore oestrogen replacement may improve urinary function in these women[14]. The third argument concerns the main topic of this paper, which is the possibility that oestrogen withdrawal at the menopause may have an adverse effect upon disease progress in MS, and that oestrogen replacement may have a beneficial effect.

We suggest that the results of this small questionnaire support this possibility, and highlight the need for further study to clarify whether the menopause and HRT really do have any objective effect upon MS. In the meantime, as there is no evidence to suggest that oestrogen has an adverse effect, no woman should be denied the benefits of HRT because she has MS.

Acknowledgments: We wish to thank the members of Action Research in Multiple Sclerosis who kindly agreed to complete our questionnaire.

References

1 Magos AL, Studd JWW. Effects of the menstrual cycle on medical disorders. *Br J Hosp Med* 1985;**33**:68-77
2 Korn-Lubetski I, Kahana E, Cooper G, Abramsky O. Activity of multiple sclerosis during pregnancy and puerperium. *Ann Neurol* 1984;**16**:229-31
3 Nelson LM, Franklin GM, Jones MC. Risk of multiple sclerosis exacerbation during pregnancy and breast feeding. *JAMA* 1988;**259**:3441-3
4 Poser S, Poser W. Multiple sclerosis and gestation. *Neurology* 1983;**33**:1422-7
5 Thompson DS, Nelson LM, Burns A, Burks JS, Franklin GM. The effects of pregnancy in multiple sclerosis: a retrospective study. *Neurology* 1986;**36**:1097-9
6 Weinschenker BG, Hader W, Carriere W, Baskerville J, Ebers GC. The influence of pregnancy on disability from multiple sclerosis. *Neurology* 1989;**39**:1438-40
7 Kurtzke JF. Further notes on disability evaluation in multiple sclerosis, with scale modifications. *Neurology* 1965;**15**:654-61
8 Matthews WB. Demyelinating disease. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *The Oxford textbook of medicine*, 2nd edn. Oxford: Oxford Medical Publications, 1987:21.211-21.218
9 Sridama V, Pacini F, Yang SL, Moawad A, Reilly M, DeGroot LJ. Decreased levels of helper T cells. A possible cause of immunodeficiency in pregnancy. *N Engl J Med* 1982;**307**:352-6
10 Manyonda IT, Pereira RS, Makinde V, Brincat M, Varma RT. Effect of 17β-oestradiol on lymphocyte subpopulations, delayed cutaneous hypersensitivity responses and mixed lymphocyte reaction in post menopausal women. *Maturitas* 1992;**14**:201-10
11 McKinlay SM, Jeffreys M. The menopausal syndrome. *Br J Prev Soc Med* 1974;**28**:108-15
12 Studd J, Savvas M, Watson N, Garnett T, Fogelman I, Cooper D. The relationship between plasma estradiol and the increase in bone density in postmenopausal women after treatment with subcutaneous hormone implants. *Am J Obstet Gynecol* 1990;**163**:1474-9
13 Brincat M, Moniz CJ, Studd JWW, *et al.* Long-term effects of the menopause and sex hormones on skin thickness. *Br J Obstet Gynaecol* 1985;**92**:256-9
14 Versi E, Cardozo LD. Oestrogens and lower urinary tract function. In: Studd JWW, Whitehead MI, eds. *The menopause*. Oxford: Blackwell Scientific, 1988:76-84

(Accepted 19 February 1992)